Sex-Dependent Alterations of Apoptotic Processes in Alzheimer's Disease Revealed by Large-Scale Single-Cell Transcriptomics

Luxembourg Centre for System Biomedicine

Mohamed Soudy[1], Sophie Le Bars[1], Enrico Glaab[1]

1 *Biomedical Data Science Group, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg*

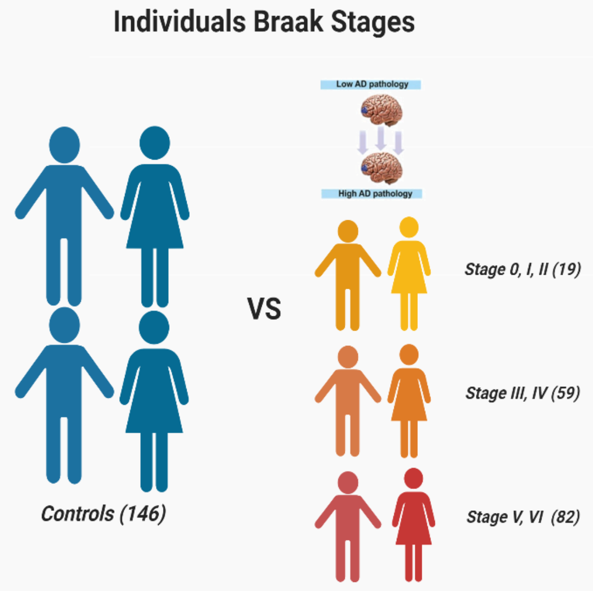
Abstract

- Alzheimer's disease exhibits significant sex differences in prevalence, progression, and clinical manifestations, but the underlying molecular mechanisms remain unclear.
- We conducted systems-level bioinformatics analyses on a large-scale single-cell transcriptomic atlas of Alzheimer's disease, derived from 427 human prefrontal cortex samples with varying AD pathology.
- Male astrocytes showed sex-specific modulation of **cell death pathways** involving regulatory genes like ***SGK3*** and ***ERBB4***, while female astrocytes had changes in **Wnt signaling** and **cell cycle pathways.**
- The gene ***RPTOR*** was identified as a key male-specific regulator in astrocytes, highlighting its role in sex-dependent expression changes in Alzheimer's disease.

Background

- Alzheimer's disease (AD) exhibits striking heterogeneity in prevalence, progression, and manifestation between the sexes, with women bearing a disproportionate burden of the disease [1]
- Accumulating evidence from epidemiologic, clinical, and biological studies underscores the importance of understanding these sex differences in AD [2, 3]

Data

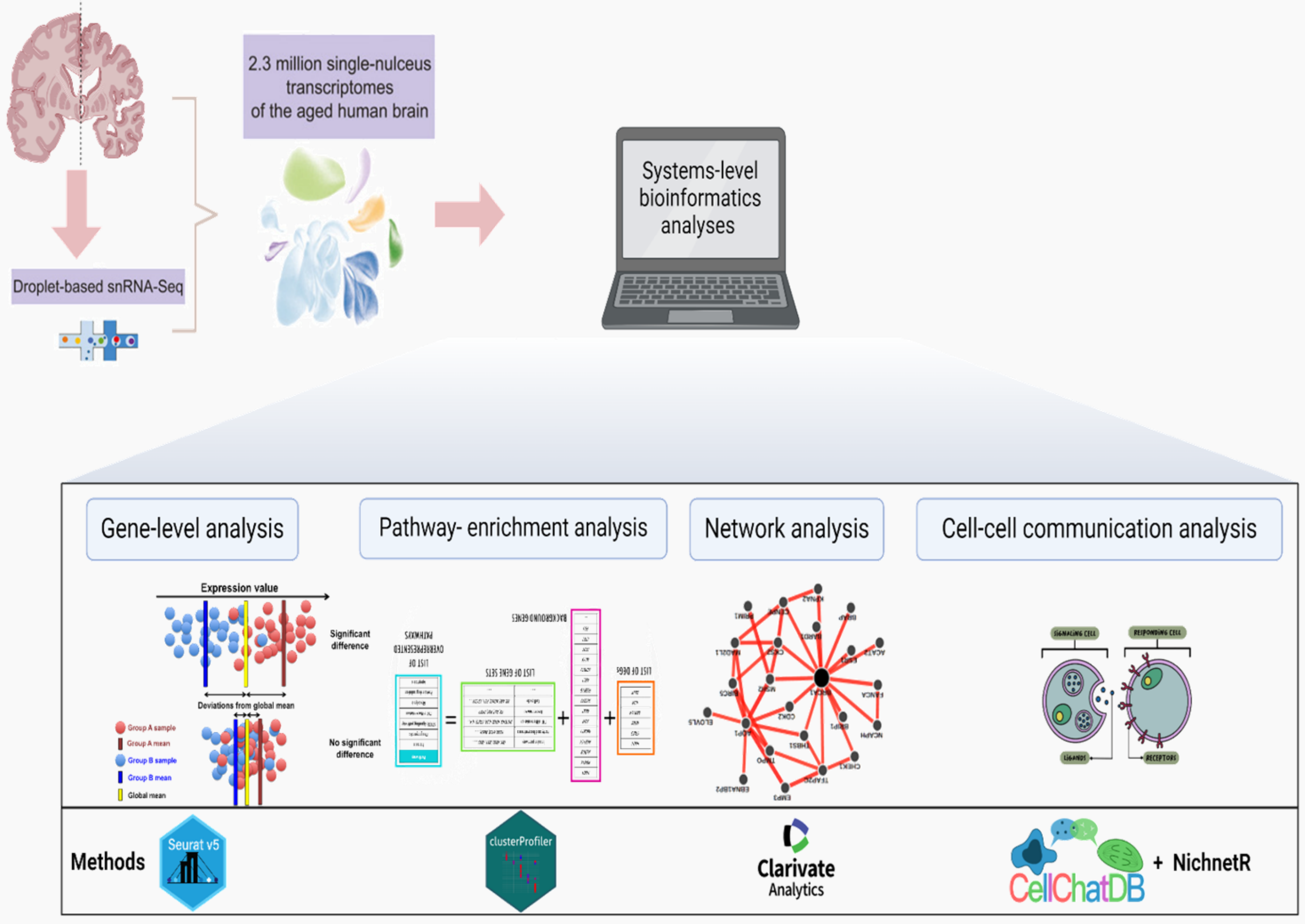


Objectives

- Investigate the sex differences in Alzheimer's disease by analyzing a large-scale single-cell transcriptomic atlas of the human prefrontal cortex.
- Build a cell type-specific and sex-specific differential expression, pathway analysis, gene regulatory networks and cell-cell communication to identify sex-dependent changes in the data.

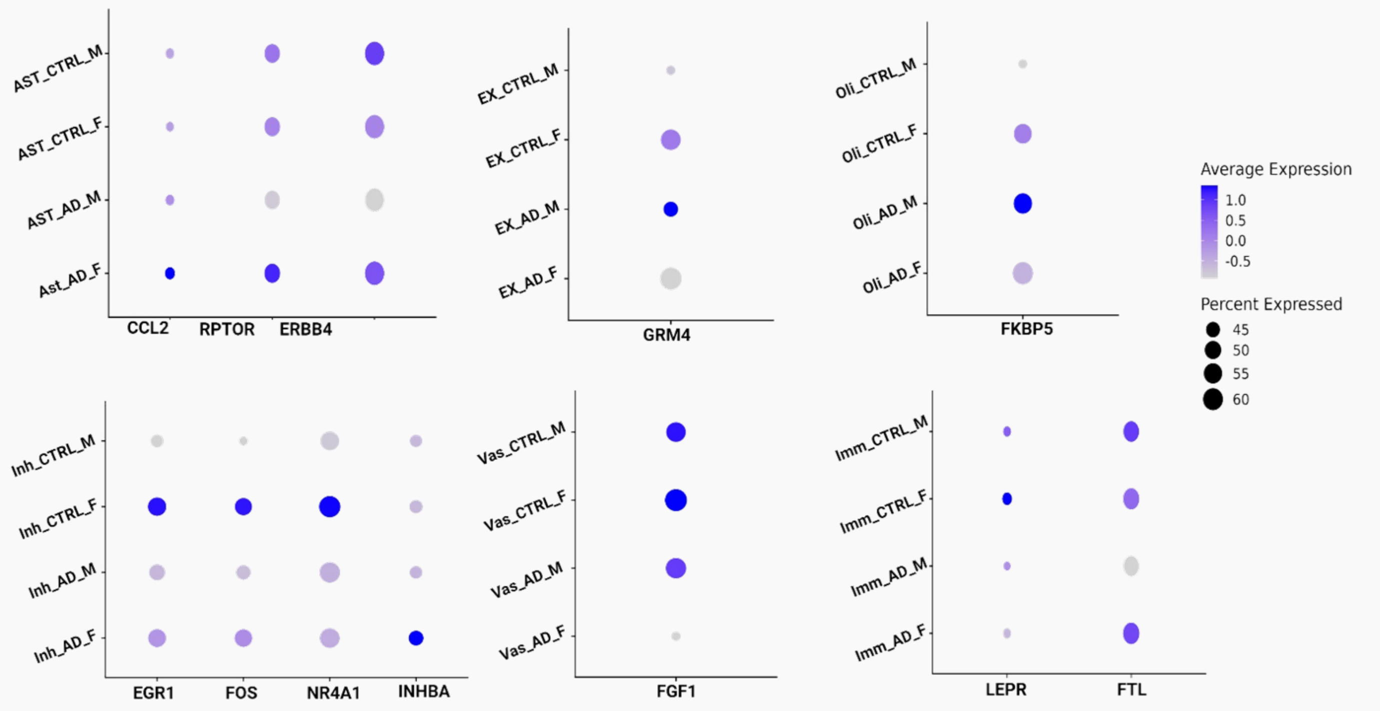
Methods

Gene-Level Analysis: Differential expression analysis was performed using Seurat's Poisson method. DEGs were classified as male-specific, female-specific, shared (same log2FC sign) or contrasting (opposite log2FC signs).

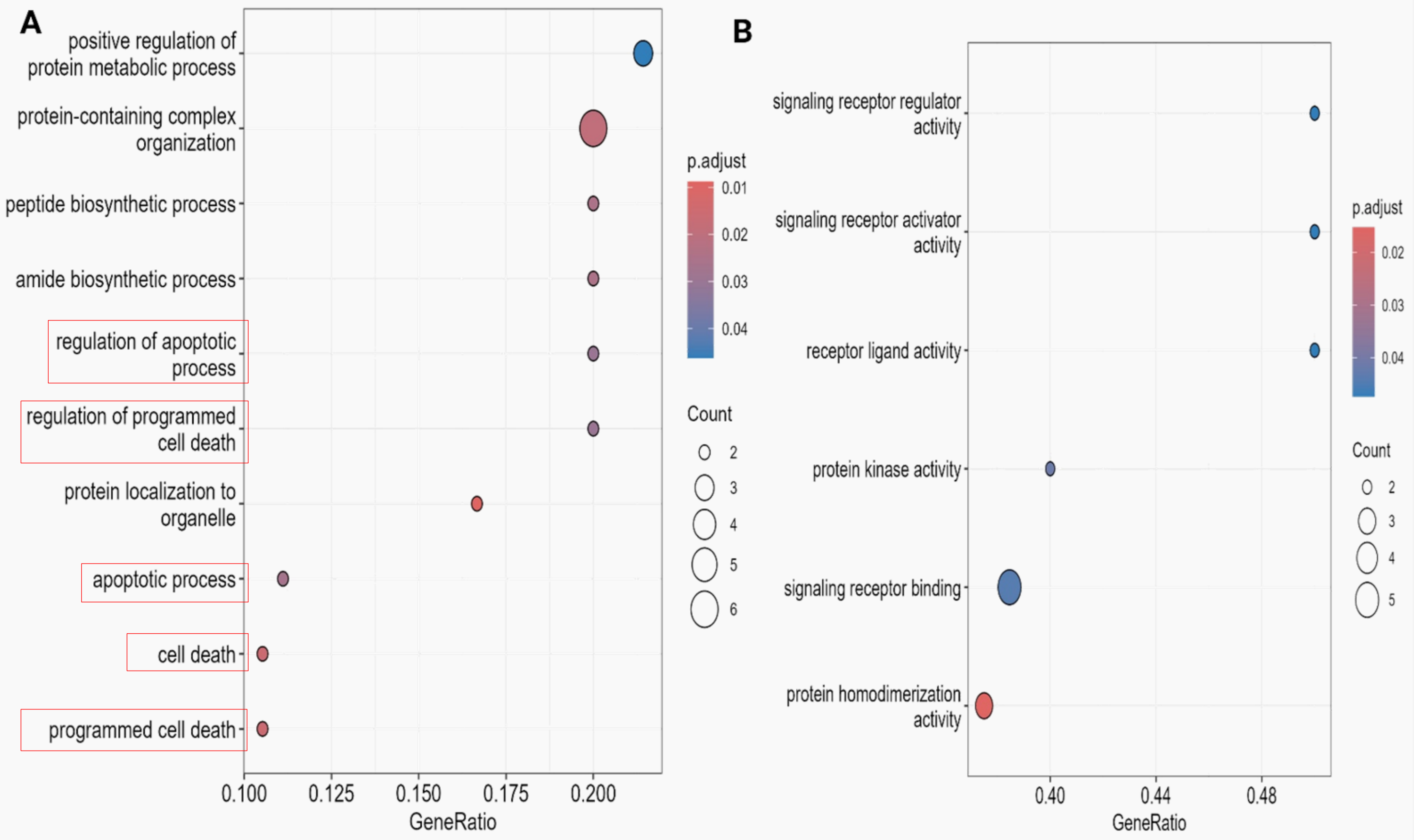


Result

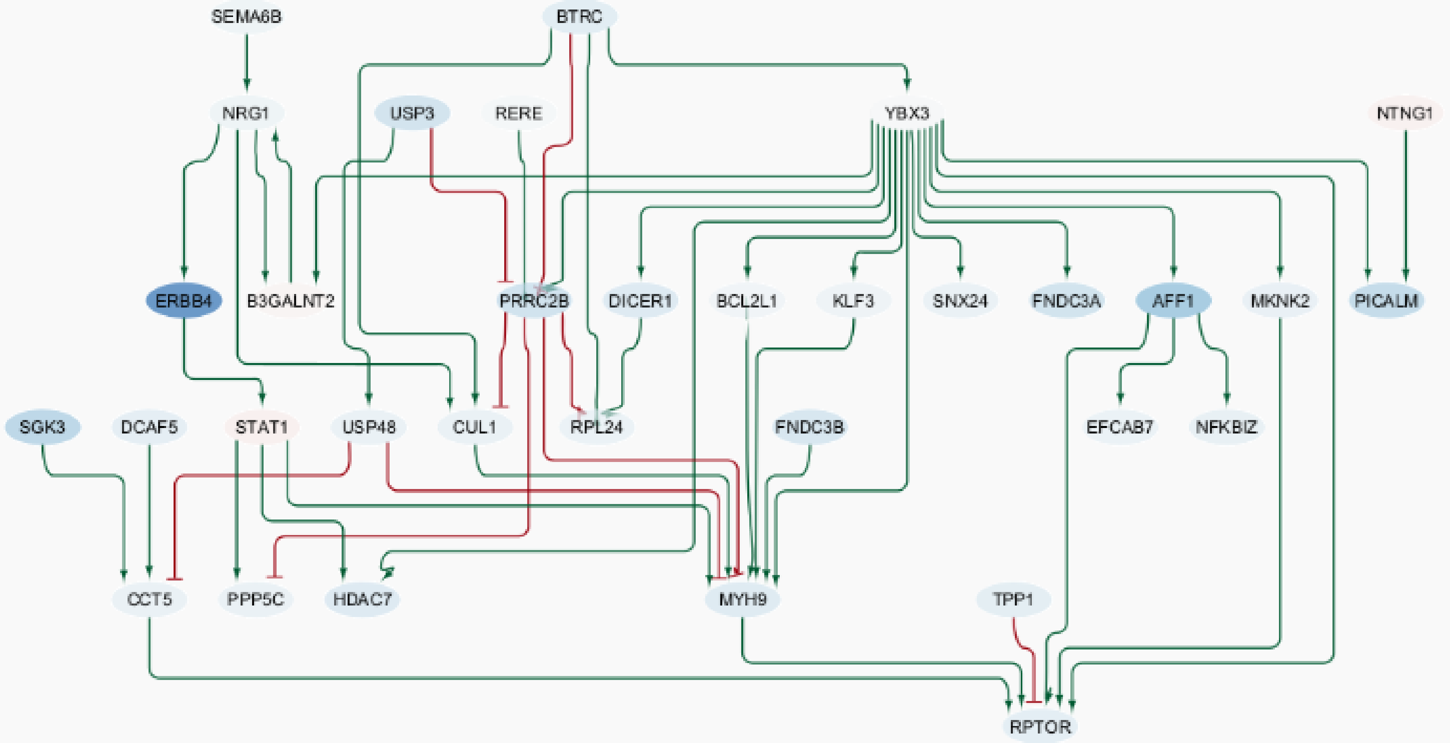
Key sex-dimorphic genes across specific cell types in AD



Enriched Gene Ontology (GO) terms in male astrocytes



Graph representation of the GRN in astrocytes for male AD patients



Conclusion

- Gene level analysis revealed that sex-specific DEGs in astrocytes, such as ***ERBB4*** and ***SGK3*** in males and ***CCL2*** and ***INHBA*** in females, highlight the importance of considering sex-specific gene expression in understanding AD's molecular landscape.
- Pathway analysis reveals sex-dependent differences in cellular responses to AD, with males showing changes in apoptosis and females in **Wnt signaling**, cell cycle, and **calcium ion transport pathways.**
- Network and cell-cell communication analysis reveals sex-specific regulatory hubs, with ***NRG1*** and ***CCT5*** in males and ***LRP1*** in females, alongside distinct intercellular signaling patterns involving **apoptosis** in **males** and **Wnt** and **calcium** pathways in **females**, suggesting differential contributions to AD progression.***CDKN1A*** (p21) is emerging as a regulator of α-synuclein aggregation in PD

[1] R. S. Wilson, E. Segawa, P. A. Boyle, S. E. Anagnos, L. P. Hizel, and D. A. Bennett, "The natural history of cognitive decline in Alzheimer's disease," Psychol. Aging, vol. 27, no. 4, pp. 1008–1017, Dec. 2012, doi: 10.1037/a0029857.

[2] A. Grubman et al., "A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation," Nat. Neurosci., vol. 22, no. 12, pp. 2087–2097, Dec. 2019, doi: 10.1038/s41593-019-0539-4.

[3] Molecular characterization of selectively vulnerable neurons in Alzheimer's Disease - PMC." Accessed: Sep. 09, 2024. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7854528/